

Vaccines and Therapeutics Subcommittee: Report to Tick-Borne Disease Working Group

Presenters:

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**Tick-Borne Disease
Working Group**

Meeting #4

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Disclaimer



Information and opinions are those of the presenter(s) and do not necessarily reflect the opinions of Working Group members or the U.S. Department of Health and Human Services.

Background



The subcommittee focused on vaccines and therapeutics distributed primarily through availability in the pharmacy, including compound pharmacies (present or recent past).

The committee also considered products in clinical development.

Both **antimicrobial and non-antimicrobial** therapeutics were analyzed, assessing their use for **pathogens** and **symptom management** in Lyme disease in humans.

Subcommittee Members



- **Dennis M. Dixon**, PhD, Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Diseases, NIAID/NIH/HHS (Co-Chair)
- **Robert P. Smith**, MD, MPH, Director, Division of Infectious Diseases, Department of Medicine, Maine Medical Center (Co-Chair)
- **Felipe C. Cabello**, MD, Professor of Microbiology and Immunology, New York Medical College
- **Monica E. Embers**, PhD, Assistant Professor; Director, Vector-Borne Diseases Core, Division of Bacteriology and Parasitology, Tulane National Primate Research Center
- **Maria Gomes-Solecki**, DVM, Associate Professor, Department of Microbiology, Immunology and Biochemistry, University of Tennessee Health Science Center
- **Utpal Pal**, PhD, Professor and Director, Veterinary Medical Sciences Graduate Program, University of Maryland College of Agriculture and Natural Resources
- **Stanley A. Plotkin**, MD, Emeritus Professor of Pediatrics, University of Pennsylvania
- **Juan C. Salazar**, MD, MPH, FAAP, Physician in Chief and Executive Vice President of Academic Affairs, Connecticut Children's Medical Center; Professor and Chair, Department of Pediatrics, University of Connecticut Health Center
- **Leigh Ann Soltysiak**, MS, Owner, Principal Commercialization and Strategy Consultant, Silverleaf Consulting, LLC

Methods



- The subcommittee held 10 teleconference meetings.
- Scientific and clinical experts presented clinical data and/or current clinical practice summaries describing vaccines and therapeutics in use or under investigation.
- Topics of/presenters for our meetings were as follows:
 - 2/28 Overview of Vaccines for Humans, Stanley Plotkin, MD
 - 3/7 Vaccines for Reservoir Hosts, Maria Gomes-Solecki, DVM
 - 3/14 Consensus Verification
 - 3/21 Veterinary/Human Vaccination Strategies, Richard Marconi, PhD
 - 3/28 Tick-Bite Targeted Vaccines, Utpal Pal, PhD
 - 4/4 Non-Antimicrobial Therapeutics, John Aucott, MD & Richard Horowitz, MD;
Antimicrobial Therapeutics in Development, Felipe Cabello, MD & Monica Embers, PhD
 - 4/11 Antimicrobial Therapeutics, Robert Smith, MD, MPH & Juan Salazar, MD, MPH, FAAP
 - 4/18 Consensus Gathering
 - 4/25 Vote on Potential Actions and Draft Report
 - 5/4 Submission of Report

Methods



Vaccines and Therapeutics Subcommittee's record-keeping was outsourced to a third-party writer.

- A summary (report) was completed at the end of each meeting.
- Subcommittee consensus occurred at the two consensus meetings after review of the draft report and slide presentation.
- There was agreement on the methods throughout the subcommittee process.
- All participants voted unanimously to approve:
 - the list of potential actions and
 - the final report.

Potential Actions: Vaccines



Overview

- A human vaccine for Lyme disease (LYMErix) was briefly available on the market with efficacy and safety that equaled or exceeded that of other licensed vaccines (approximately 80%, with boosters likely required); clinical trials did not include children.
- The vaccine was withdrawn in 2002 due to market reasons.
- At least one human Lyme vaccine is in clinical development in the U.S. and in Europe.
- Multiple other human, reservoir targeted, and tick antigen-targeted vaccines are being explored.

Challenges

1. Scientific (achieving optimal safety and efficacy)
2. Overcoming the legacy of the LYMErix vaccine

Vaccines: Conceptual Approaches



- Human targeted
 - Bacterial antigens: OspA, OspB, OspA/OspC chimerotypes¹
 - Example: Valneva's six-valent OspA minus the hLFA-1 epitope²
 - Tick salivary antigens
- Reservoir targeted
 - Potential antigens: OspA, tick salivary proteins, etc.
 - Oral bait delivery to mice, using *Escherichia coli* or *Vaccinia* vectors

¹ OspA = outer surface protein A; OspB = outer surface protein B; OspC = outer surface protein C

² hLFA-1 = human leukocyte function antigen-1

Vaccines: New OspA-Based Candidate



- Valneva's six-antigen recombinant protein lacking hLFA-1
- Covers the six most common serotypes in the U.S. and Europe
- Phase I trial completed
 - No safety concerns
 - Valneva press release, dated March 19, 2018: "Good OspA-specific IgG Ab response to all serotypes after 3 vaccinations"¹

¹ IgG Ab = immunoglobulin G antibody

Barriers to Acceptance of a Lyme Disease Vaccine



- Public: Concerns regarding safety and efficacy; cost (insurance coverage); convenience (e.g., durability of immunity and need for booster vaccinations)
- Industry: Concerns regarding commercial withdrawal of LYMErix
- Public health: regulatory support; relative public health priority versus other vaccine-preventable infections; potential for “false sense of security”

Proposed Responses to Barriers



- Epidemiologic rationale for re-introduction of a Lyme disease vaccine
 - Expanding range of vector
 - Increasing number of cases
 - Rising health care costs
- Clinical trials, in addition to demonstrating efficacy and safety, should include children and determine the timing of booster vaccinations, if needed.
- Before introduction, involvement in the process by public and private entities (i.e., patients, medical providers, payers, academia, public health agencies, industry) is needed to improve communication, address concerns, and develop broad-based support.

Vaccines: Potential Actions



- Field trials have demonstrated proof of principle for use of OspA-based vaccination of rodents as a possible strategy for interrupting transmission of *Borrelia burgdorferi* in the environment.¹
 - Other antigens, such as tick salivary proteins, may also have potential.
- **Challenges:** Logistics and cost may limit marketability of field-based interventions.
- **Potential actions:** Support additional studies and/or modeling of effectiveness in different residential/ecological settings.

¹ *Borrelia burgdorferi* is the new name for the species previously known as *Borrelia burgdorferi*

Therapeutics: Antimicrobials for Lyme Disease



- Multiple randomized controlled trials (RCTs) in North America and Europe support the use of oral antimicrobials to treat most cases of *B. burgdorferi* infection. Antibiotics supported by these studies include:
 - Cephalosporins (i.e., cefuroxime axetil),
 - Tetracyclines (especially doxycycline),
 - Penicillins (primarily amoxicillin), and
 - To a lesser extent, macrolides (primarily azithromycin).
- Intravenous ceftriaxone, penicillin, and cefotaxime (Europe) are usually reserved for Lyme neuroborreliosis or carditis and relapsed Lyme arthritis.
- Ongoing research is exploring potential for additional antibiotic options through *in vitro* and *in vivo* (animal) studies.

Therapeutics: Antimicrobials for Lyme Disease (*cont.*)



Challenges

- Antibiotic choices are more limited for women who are pregnant or breastfeeding and for pediatric patients, and are very limited for treatment of some co-infections.
- Symptoms may persist following standard antibiotic treatments.
- RCTs to date have not demonstrated a therapeutic benefit for antibiotic treatment of PTLDS when compared to the associated adverse effects.
- RCTs of treatment for PTLDS have not included children.

Opportunities

- Research on pathogenesis of persistent symptoms in patients treated with standard antibiotics may lead to new approaches to treatment of PTLDS

Therapeutics: Non-Antimicrobials Used in Treatment of Lyme Disease



- Non-antimicrobial therapies may be administered in concert with antimicrobial therapy or for treatment of persistent symptoms following antimicrobials
- Approved therapies, within other disease states, are used to treat PTLDS symptoms, including pain, fatigue, and cognitive symptoms, as are a variety of compounded medications and herbal preparations.
- For Lyme disease-related pain, non-antimicrobial therapies approved for fibromyalgia may prove effective, including: pregabalin; duloxetine hydrochloride; milnacipran HCl.
- Lyme disease-related fatigue, often complex, may be managed with antidepressants, stimulants, sleep aids, and therapies for co-morbid conditions.
- For treatment of inflammation of Lyme arthritis, non-steroidal anti-inflammatory drugs are commonly used.
- For persistent antibiotic-refractory Lyme arthritis, methotrexate, hydroxychloroquine are used, and, if there is no response, tumor necrosis factor (TNF) inhibitors are recommended.

Non-Antimicrobials (*cont.*)



Challenges

- The mechanisms of pathogenesis of persistently symptomatic Lyme disease and post-treatment Lyme disease syndrome (that is, immune response, cross-reactivity, autoimmunity, bacterial persistence) are not well understood.
- There is a lack of clinical data on the overall effectiveness for symptom relief for many non-antimicrobial therapeutics for Lyme disease and PTLDS.

Opportunities

- Continued research to determine the pathogenesis of symptoms in late Lyme disease and PTLDS could improve treatment options for patients with those symptoms.

Summary: Potential Actions



Prioritized Issue #1: Human Vaccines to Prevent Lyme Disease

Support for availability of human vaccine(s) for prevention of Lyme disease is a top priority.

It is critical to prepare the market for a Lyme disease vaccine through proper disease awareness and education.

Potential Actions:

- Identify current barriers to public and industry acceptance of vaccines for Lyme disease, and address concerns as part of the process.
- Support continued development for human Lyme disease vaccines.

Summary: Potential Actions (*cont.*)



Prioritized Issue #2: Therapeutics for PTLDS

Potential Actions:

- Continued research into the pathogenesis (that is, immune response, cross-reactivity, autoimmunity, bacterial persistence) of persistent symptoms in patients who have received standard treatment regimens